REMARKS

This is a full and timely response to the Final Office Action mailed August 20, 2008. Upon entry of this response, claims 48, 55, 62-70, 72-76, and 78-81 are pending in the application.

In this response, claims 48, 55, 62-70, 72-76, and 78-81 have been canceled without prejudice or disclaimer, and new claims 82-100 are herein submitted for entry and examination.

Applicants respectfully request that the new claims being filed herewith be entered and request that there be consideration of all pending claims in light of the following remarks.

CLAIMS

Rejections under 35 USC §112, first paragraph

Claims 48, 55, 62-70, 72-76, and 78-81 are herein canceled and replaced by new claims 82-100, thereby rendering the rejections under 35 U.S.C. §112, first paragraph moot. However, to avoid the same issues being raised once again with respect to the new claims submitted herein, Applicants now also fully address the specific issues raised by the Examiner in the Final Office Action of August 20, 2008.

The rejection of claims 48, 55, 62-70, 72-76, and 78-81, made in paragraph 9 of the Office Action mailed July 30, 2007, under 35 U.S.C. §112, first paragraph, as being non-enabled with regard to scope, was maintained by the Examiner.

The Examiner alleged (Final Office Action, page 4) that:

> "....[C]ontrary to Applicants' assertion, the third paragraph on page 28 of the specification as originally filed, describes that MAb B5 is an IgG3 antibody which was raised against *Neisseria meningitidis* H44/76 immunotype L3 *galE*. The Office agrees with Applicants that MAb B5 recognizes L1, L3, L7, L8, L9, L10, L11 and L12 immunotypes of is an IgG3 antibody *Neisseria meningitidis*. However, as presented currently, *none of the instant claims* recite that the LPS inner core comprised in the recited immunogenic composition is a conserved LPS inner core and that it contains MAb B5-specific inner core epitope of *Neisseria meningitidis* H44/76 immunotype L3 *galE*. The LPS inner core comprised in the immunogenic composition administered in the method of claims 48, 55, 62-64, 66-68, 70, 72-74, 76, and 78-80, as presented currently, is not limited to *Neisseria meningitidis* H44/76 immunotype L3 *galE*."

Applicants emphasize that the scope of the new claims submitted herein is drawn to the *Neisseria meningitidis* lipopolysaccharide inner core epitope that is defined in the specification as being specifically reactive with the monoclonal antibody B5. The antibody identity is fully provided in the specification, and in new claim 82, by reference to the parent hybridoma,

including the appropriate deposit accession number. The epitope may be further structurally defined by: (i) the structural formula, (ii) a statement that places the phosphoethanolamine group that is central to the epitopic site as being attached to the 3-position of the heptose II moiety of the claimed structure, and (iii) that the claimed epitope is specific to the *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11, and L12, but not to the immunotypes L2, L4, L5, and L6.

The claimed epitope, and the region of the inner core of the lipopolysaccharide of Neisseria meningitidis immunotype L3, are fully defined in the specification as filed, and therefore, the new claims as submitted herein contain no new matter. For example, support for the definition of the region of the inner core and the epitope within may be found throughout the specification as filed, such as at pages 8-9 of the specification, which are reproduced as follows:

> "Preferably the principal immunogenic component is a conserved epitope on the LPS inner core recognized by an antibody termed B5 herein. The preferred epitope of the invention is thus any epitope recognized by the B5 antibody.
>
> Preferably the immunogenic component is a conserved epitope on the LPS inner core defined by the presence of a phosphoethanolamine moiety (PEtn) linked to the 3-position of HepII. The β-chain heptose, of the inner core, or is a functional equivalent thereof. In this respect, where the context permits, HepI and HepII refer to the heptose residues of the inner core oligosaccharide which respectively are proximal and distal to the lipid A moiety of the neisserial LPS, without being necessarily tied to the general formula given above.
>
> Preferably this epitope comprises a glucose residue on HepI, the α-chain heptose residue. While this glucose is not necessary for B5 binding, it is required for optimal recognition.
>
> The principal immunogenic component of the present invention is preferably an epitope on the LPS inner core which comprises an N-acetyl glucosamine on HepII. The presence of N-acetyl glucosamine is required for optimal recognition by B5.
>
> Preferably the principal immunogenic component comprises both the N-acetyl glucosamine on HepII and a glucose residue on HepI.
>
> The immunogenic component of the present invention is typically only limited by the requirement for a phosphoethanolamine moiety (PEtn) linked to the 3-position of HepII of the inner core, which is required for B5 reactivity. The structure of the inner core may be modified, replaced, or removed, as necessary, to the extent that these are not needed. Similarly, any outer core structures may be modified or deleted, to the extent that structural elements are not needed."

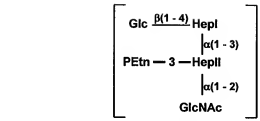
Applicants acknowledge the Examiner's observation that the claimed epitope was first identified in a *galE* mutant of *Neisseria meningitidis* strain H44/76, according to the data taught in the specification of the present application. However, the cross-reactivity of monoclonal

antibody B5 with other *Neisseria meningitidis* strains, ***including those that do not have the galE mutation***, clearly indicate that the genotype of strain H44/76 *galE* is not a unique identifier for the epitope as disclosed and claimed in the present application. Stating the genotype of the *galE* mutant of *Neisseria meningitidis* strain H44/76 merely serves to identify one experimental source for the region of the lipopolysaccharide inner core. It does not serve to characterize the epitope itself in any way.

The new claims 92-99 are drawn to a method of eliciting an antibody by administering an ***immunogenic composition*** comprising a region of a lipopolysaccharide inner core, the structure of which is shown, combined with the statement that said region ***can be found*** in the inner core of the *Neisseria meningitidis* strain H44/76 *galE*. The clear meaning and intent of this language is that the identified region of the inner core is a component of the immunogenic composition, ***not*** that the immunogenic composition ***is*** the entire inner core of the *Neisseria meningitidis* strain H44/76 *galE* strain (although use of the term "comprising" does not preclude the use of the entire inner core of the *Neisseria meningitidis* strain H44/76 *galE*, or a fragment thereof that includes the identified region, as an immunogenic composition).

Reference to the immunogenicity of the composition clearly distinguishes the identified region of the inner core from another region, also of the inner core, that is non-immunogenic. What is relevant in the context of the scope of the claims in the present application is a definition of the epitope that unequivocally distinguishes the claimed epitope from any other epitopic structure within the overall inner core structure, and in such a manner as to avoid confusion with a non-immunogenic strain of *Neisseria* as the source of immunogens. Applicants, therefore, assert that by providing structural and functional descriptors, the claimed epitope is now fully and adequately defined in all the newly submitted claims within the understanding of the requirements of 35 U.S.C. §112, first paragraph.

The new claims 92-99 are drawn to a method of eliciting an immune response in a recipient subject by administering to the subject an immunogenic composition that consists essentially of the lipopolysaccharide inner core epitope of *Neisseria meningitidis* immunotype L3 strain H44/76 *galE*, where the inner core epitope is selectively reactive with the monoclonal antibody B5 produced by the hybridoma deposited with the accession number IDAC 260900-1, and. The inner core ***region*** is characterized as having the formula:



,

while the inner core ***epitope*** is a phosphoethanolamine (PEtn) group linked to position 3, but not to position 6 or 7, of the HepII moiety of the inner core region, the method eliciting in the recipient subject an immune response that generates an antibody that can bind selectively to the lipopolysaccharide inner core epitope of the *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11, and L12, but not to immunotypes L2, L4, L5, and L6.

The Examiner, in the Final Office Action at pages 8-9 states:

> "The progress of conjugation of a conserved inner core LPS to a protein or peptide can block the conserved serogroup-nonspecific inner core epitope or the protective inner core epitope, can alter the conformational integrity of the inner core, and/or modify the chemical structure of the inner core."

Applicants traverse this assertion in the context of the newly submitted claims. Since the subject epitope of the present application, when in an immunogenic composition, is defined as being able to elicit the generation of an antibody that specifically binds to the subject epitope, the Examiner's argument is moot with respect to any denaturation or prevention of access to the epitope by linking to a carrier molecule. In the event that the epitope is modified by a linkage to a moiety in such a way that it can no longer elicit an immune response, then by definition it is no longer an immunogenic composition within the scope of the claims submitted herein.

The Examiner, in the Final Office Action at pages 4-5 states:

> "Applicants submit that pages 25 and 26 of the instant specification describe the use of a rabbit polyclonal antibody specific for group B *Neisseria meningitidis* capsular polysaccharide obtained by immunizing a rabbit with lysates of MC58 with Freund's adjuvants and the pre adsorption of the polyclonal antibody with capsule-deficient mutant of MC58 to increase the specificity of the polyclonal antibody for the group B meningococcal capsular polysaccharide. However, the elicitation of a group B *Neisseria meningitidis* capsule-specific antibody by immunization of a rabbit with lysates of MC58 that contains a plethora of antigens is not relevant to the instantly claimed method, because the active immunogenic element in the instantly recited immunogenic composition is not a capsular polysaccharide of group B *Neisseria meningitidis*."

Applicants assert that any reference to a rabbit polyclonal antibody with respect to claims 48, 55, 62-70, 72-76, and 78-81 is now moot due to cancellation of these claims, nor relevant to the new claims as herein submitted.

The Examiner has alleged in the Final Office Action mailed August 20, 2008 (and repeated from the Office Action mailed July 30, 2007) that:

"With regard to the Office's position that the infant rat model used in the passive protection experiment using an avirulent *galE* strain of *Neisseria meningitidis* as the challenging or infecting strain is of little prophylactic significant, Applicants submit the following arguments:

(a) Animal infection models are valuable for the development and preclinical assessment of meningococcal vaccines. It is only in animal models that interactions of the organism with the innate, humoral and cellular immune systems can be assessed.

(b) Infection of infant rats has been used to assess passive protection provided by sera raised against vaccine candidates or human vaccine sera. The specification of the present invention provides a valid recognized animal model that need not contain an example in human subjects, because the invention is disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation.

(c) The infant rat model is recognized as correlating to passive protection. The Office did not provide evidence that the model does not correlate. However, whether or not infection of infant rats has been used to assess passive protection provided against a virulent strain of *Neisseria meningitidis* by sera raised against vaccine candidates or human vaccine sera is not the issue. The issue to be addressed is the use of an art-known avirulent strain of *galE* mutant strain of *Neisseria meningitidis* as the challenging/infecting strain in the infant rat model of passive protection. Contrary to Applicants' assertion, in paragraph 9 of the Office Action mailed 07/30/07, the Office set forth a detailed *prima facie* case of lack of enablement by establishing that the infant rat model used in passive protection against a *galE* strain of *Neisseria meningitidis* that has been demonstrated in the art to be avirulent is of no prophylactic significance in a human or non-human host. That part of the Office's rejection is reproduced herein below:

Furthermore, the limitation 'host' in the base claims encompasses a mammalian and a non-mammalian host, a human host including a human child, or a non-human host such as an infant rat. The phrase in the base claims 'antibody . . . capable of conferring passive protection against a *galE* mutant of an L3 immunotype of *Neisseria meningitidis* strain' leaves open the specific host(s) in whom the antibody is capable of conferring passive protection against a *galE* mutant of an L3 immunotype of *Neisseria meningitidis* strain. The conferring of passive protection against a *galE* mutant of an L3 immunotype of *Neisseria meningitidis* strain does not exclude but includes passive protection being conferred to a human host or an infant rat host against a *galE* mutant of an L3 immunotype of *Neisseria meningitidis*. The need for passive protection against any immunotype or strain of *Neisseria meningitidis* in a given host exists only if said immunotype or strain is virulent or pathogenic. The state of the art at the time of the instant invention documented that *galE* mutation dramatically alters the virulence potential of meningococci and that *galE* mutants of *Neisseria meningitidis* are "both serum sensitive and **avirulent** for infant rats", the avirulence being independent of encapsulation. See the first full sentence in left column on page 164 and the first two full sentences under 'Discussion' of Vogel *et al. (Microbiol. Immunol.* 186: 159-166, 1997) (Vogel *et al.,* 1997). Vogel *et al.* (1997) further discussed

a previous study by Vogel *et al. Med. Microbiol. Immunol.* 185: 81-87, 1996 (Vogel *et al.*, 1996) on the meningococcal virulence in the infant rat model, which demonstrated that only the wild-type strains exhibited the capacity to spread systemically. See left column on page 160 of Vogel *et al.* (1997). The *galE* mutant of *Neisseria meningitidis* lacking the terminal three sugars of the LPS was shown to be avirulent despite the presence of a capsule, and was shown not to spread systemically into the blood stream even in animals infected with 10^8 CFU. No *galE Neisseria meningitidis* could be reisolated from the blood of even those animals that received a challenge dose of 10^8 CFU of *galE Neisseria meningitidis*. See paragraph bridging pages 85 and 86; paragraph bridging left and right columns on page 83; and right column of page 83; and Figure 1 of Vogel *et al.* (1996). The only hosts in which the only antibody, i.e., the monoclonal B5 antibody, that is evaluated in the instant specification for its ability to confer the supposed 'passive protection' against *galE* mutant of an L3 immunotype of *Neisseria meningitidis*, are infant rats. It should be noted that the challenge innoculum of the *galE* mutant of *Neisseria meningitidis* that Applicants used in their infant rat model is also 1×10^8 CFU (see the paragraph bridging pages 53 and 54 and the paragraph bridging pages 57 and 58 of the instant specification), a dose that is identical to the dose of 10^8 CFU of *galE Neisseria meningitidis* that is shown by Vogel *et al.* (1996) not to disseminate systemically in the infant rat model. Therefore, at least in infant rat hosts, the recited antibody cannot be characterized as having 'passive protective capacity' against *galE* mutant of an L3 immunotype of *Neisseria meningitidis*. An animal model of passive protection that uses an avirulent *Neisseria meningitidis* as the challenging or infecting strain is of little prophylactic significance in said animals. Furthermore, how this supposed passive protection in an avirulent infant rat animal model relates to or correlates with passive protection in a human adult or infant host against homologous *galE* mutant of an L3 immunotype of *Neisseria meningitidis*, or a heterologous virulent, invasive, wild type L3 immunotype of *Neisseria meningitidis*, is neither disclosed nor known. The rate of occurrence of *galE* mutants among naturally occurring carrier or clinical isolates of L3 immunotype *Neisseria meningitidis* is not known or disclosed.

Thus, the Office supported its rejection with the teachings from the art, i.e., teachings of Vogel et al. (Microbiol. Immunol. 186: 159-166, 1997) (Vogel et al., 1997) and Vogel et al. Med. Microbiol. Immunol. 185: 81-87, 1996 (Vogel et al., 1996). Applicants have provided no substantive arguments or evidence to show otherwise, let alone address the teachings of Vogel et al. (1997) and Vogel et al. (1996). An infant rat model that uses a **virulent** strain of Neisseria meningitidis is considered by those skilled in the art to be valuable for the development and preclinical assessment of meningococcal vaccines. However, an infant rat model of passive protection that uses an art-established **avirulent** *galE* mutant strain of *Neisseria meningitidis* has not been correlated with passive protection in a human adult or human infant host within the instant specification or in the state of the art."

In response to the Examiner's maintained position, Applicants argue that the experiment, as described in the present application with regard to the use of the infant rat model, clearly

demonstrates that the B5 monoclonal antibody is capable of reducing the bacterial load (bacteremia) of *Neisseria meningitidis galE* in the infant rat blood system when the bacteria are co-administered with the monoclonal antibody B5. This result is evident in Fig. 13 of the application, and it is immaterial as to whether the injected bacteria are virulent or not. The results show that a control bacterial load in the rat blood was 10^6 cfu/ml 24 hrs after initial introduction, but only about 1% thereof when co-injected with the monoclonal antibody B5.

The question of virulence in the context of *Neisseria meningitidis* is only of significance with regard to whether the bacteria can survive infecting a host cell, proliferating therein, and then re-entering the blood stream. Once in the blood stream, the antibodies present may then attack the bacteria and reduce their titer. However, if the amount of antibody delivered to the infant rats is over-whelmed by the population of co-administered bacteria, or produced by proliferation of a virulent strain, then the protective capacity of the antibody will be reduced or eliminated, resulting in a runaway infection by the virulent strain, or failure to completely clear a bacteremia of a non-virulent strain, as in the case of the experiment described in the present application.

The Examiner has overlooked that the infant rat experiment of the present application showed only that the monoclonal antibody B5 is capable of reducing the viable bacterial load under *in vivo* conditions. When the result of one study differs from the results of another, this may warrant further experimentation rather than merely hypothesizing as to the causes of differences, as requested by the Examiner. When experimental conditions between two studies differ, as is the case of the present disclosure when compared to those of the cited reference Vogel, an explanation of the differing results is meaningless in the absence of further experimentation to resolve the differences.

The pertinent point from the experiment, ***as described in the present application***, is that a control infant rat has bacteremia in the absence of the B5 antibody, and a significantly reduced bacteremia in its presence. The argument presented by the Examiner addresses the issue in terms of avirulence versus virulence, and ignores the clear experimental results of bacterial load clearance by the antibody compared to the control with no antibody. Accordingly, Applicants reassert that bacterial clearance by the antibody B5 was clearly demonstrated under *in vivo* conditions. Applicants further note, however, that the new claims, as submitted herein, make no reference to passive immunity. Examiner's rejection with respect to this aspect of the Office Action is, therefore. moot in the context of the new claims.

The Examiner, in the Final Office Action mailed August 20, at pages 7-9, addresses the issue of an alleged lack of enablement of inner core *Neisseria* LPS conjugates having the required function by stating:

> "With regard to the issue of lack of enablement of inner core *Neisseria* LPS conjugates having the required function, Applicants point to the generic description on page 13 of the specification and state that this part of the specification describes that: (a) the 'immunogenic components' of the vaccine 'may be' conjugated to homologous or heterologous proteins; and (b) the 'immunogenic component of the present invention forms a saccharide peptide conjugate'. With this, Applicants conclude that the specification enables an 'immunogenic composition comprising an inner core of a *Neisseria* LPS conjugated to a protein or peptide'. However, a mere statement in the specification that 'immunogenic components' of the vaccine 'may be' conjugated to a homologous or heterologous proteins; and that the 'immunogenic component of the present invention forms a saccharide peptide conjugate' is not sufficient to enable the claimed method which is required to elicit an antibody in a human or non-human host upon administration to said host an immunogenic composition comprises a first inner core of a *Neisseria* LPS conjugated to a protein or peptide, wherein the antibody elicited not is only required to bind to inner core LPS of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, and but is also required to confer passive protection against a *galE* mutant of L3 immunotype of *Neisseria meningitdis*. With regard to the Office's showing of lack of enablement of an inner core of a *Neisseria* LPS comprised in the recited immunogenic composition wherein the inner core is conjugated to a protein or peptide, wherein the conjugate composition is administered to a host to elicit an antibody that is not only required to bind to inner core LPS of *Neisseria meningitdis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, and but is also required to confer passive protection against a *galE* mutant of L3 immunotype of *Neisseria meningitidis*, Applicants submit the following arguments. Applicants contend that the disclosure in the present application was followed by successful results in Meningococcal conjugate vaccines containing four of the most common types of meningococcal bacteria. Applicants submit that the FDA has approved the effective Quadrivalent Meningococcal Conjugate Vaccine (MCV4) and that a conjugate vaccine to meningococcal serogroup C is used for reducing the incidence of disease in young children in the UK. Applicants point to page 2 of the specification and state that the data provides support for the efficacy of this technology.
>
> However, the approval by the FDA of a quadrivalent non-lipopolysaccharide conjugate vaccine, or the use of a serogroup C meningococcal non-lipopolysaccharide conjugate vaccine in the UK, is irrelevant to the instant rejection. These non-conserved, serogroup-specific, nonlipopolysaccharide conjugate vaccines have no meaningful nexus or relevance with the instantly claimed method which uses a conserved inner core *Neisseria* LPS that is serogroup non-specific, that is required, upon administration in a conjugate form, to elicit an antibody in a human or nonhuman host an antibody that (i) binds specifically to inner core of lipopolysaccharide of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12; (ii) is capable of conferring passive protection against a *galE* mutant of L3 immunotype of *Neisseria meningitidis*. The enabling disclosure and the evidentiary support

have to come from the instant specification as filed. As set forth previously, the method claimed in the amended claims 64, 68, 74 and 80 used an immunogenic composition comprising an inner core of a *Neisseria* LPS of the recited structure being conjugated to a protein or peptide. However, a method of eliciting an antibody that binds to an inner core LPS of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, and that is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain comprising administering a formalin-killed, outer core-lacking *galE* mutant whole cells of *Neisseria meningitidis* H44/76 strain as disclosed in the instant specification does not enable a method of eliciting an antibody that binds to an inner core LPS of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, and is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain comprising administering an immunogenic composition comprising an inner core of any *Neisseria* LPS wherein said inner core, substantially free of outer core LPS of said *Neisseria,* is conjugated to a protein or peptide. The process of conjugation of a conserved inner core LPS to a protein or peptide can block the conserved, serogroup-nonspecific inner core epitope or the protective inner core epitope, can alter the conformational integrity of the inner core, and/or can modify the chemical structure of the inner core. With regard to the immunogenicity of inner core LPS conjugates and their ability to induce functional antibodies, page 35 of the instant specification states the following [Emphasis added]:

> Future studies will look at the safety and immunogenicity of inner core LPS-conjugates (PEtn at 3- position of HepII and alternative glycoforms) and the functional ability of the polyclonal antibodies in opsonic and serum bacterial assays, initially in mice and rabbits.

....***This is because it is not obvious from the disclosure of a method of administering a formalin-killed, outer core lacking galE mutant whole cells of Neisseria meningitidis H44/76 strain as disclosed in the instant specification will extrapolate to a method of eliciting an antibody that binds to an inner core LPS of Neisseria meningitidis immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, is capable of conferring passive protection against a galE mutant of an L3 immunotype Neisseria meningitidis strain comprising administering an immunogenic composition comprising an inner core of any Neisseria LPS wherein said inner core, substantially free of outer core LPS of said Neisseria, is conjugated to a protein or peptide.*** **[Emphasis added]** The instant specification itself at paragraph bridging pages 34 and 35 acknowledges the art known unpredictability in eliciting functional (bactericidal) antibodies by a conjugate of an *N. meningitidis* immunotype inner core oligosaccharide as reflected in the study carried out by (Verheul, A.F., et al. 199 1. Infect Immun. 59: 843-851). The lack of guidance within the instant specification when taken in combination with the unpredictability factor raises the need to engage in considerable undue experimentation. The courts have held that it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement. See Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001). Moreover, the specification must have been enabling at the time the invention was made (see In re Wright, 2 7 USPQ2d 151 0). A claim must be enabled over its whole breadth."

The Examiner, in the passage highlighted immediately above, apparently alleges that it is not obvious how the use of a formalin-killed, *galE* mutant (outer core lacking) whole cells of the *Neisseria meningitidis* H44/76 strain can extrapolate to a method of eliciting an antibody that binds to an inner core LPS of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, **and is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain**, when the method would comprise administering an immunogenic composition comprising an inner core of any *Neisseria* LPS wherein said inner core is substantially free of outer core LPS of said Neisseria, and is conjugated to a protein or peptide.

The new claims as submitted herein do not include any reference to induction of passive immunity. Applicants further note that the claimed epitope of the new claims submitted herein is ***BY DEFINITION*** able to induce the formation of an antibody able to specifically bind to the inner core epitope. If the epitope was conjugated to a peptide or other carrier that modified its structure or configuration so that it was no longer recognizable by the monoclonal antibody B5, then it would not be the epitope as claimed.

Rejections under 35 USC §112, second paragraph

1. The Examiner, in paragraph 11 of the Final Office Action mailed August 20, 2008, maintained the rejection of claims 48, 55, 70, and 76 made in paragraph 10(a) of the Office Action mailed July 30, 2007 under 35 U.S.C. §112, second paragraph, as being indefinite, and repeated the reasons for the rejection.

The Examiner stated that:

> "As set forth previously, not only claims 48 and 55, but also claims 70 and 76, continue to include the indefinite, incorrect and/or confusing limitations 'position 3 of a HepII moiety of said inner core' and 'an inner core LPS'. The limitations 'a HepII moiety of said inner core' and 'an inner core LPS' convey that the recited *Neisseria* LPS has more than one HepII moiety in the inner core and more than one inner core in the LPS. However, all through the specification, the application describes the *Neisseria* LPS to have no more than one inner core and no more than one HepII moiety. See pages 7 and 8 of the instant specification for example, which include the recitations: 'the 3-position of HepII' and 'the inner core . . . of *Neisseria meningitidis* LPS'. To obviate the rejection, it is suggested that Applicants replace the limitation 'a HepII moiety' with the limitation --HepII moiety-- and the limitation 'a . . . .. inner core' with --the inner core--."

Although claims 48, 55, 70 and 76 are canceled herein, and therefore this rejection has been rendered moot, Applicants note that the new claims submitted herein do use the definite

article as suggested by the Examiner, or otherwise clearly refer to *the* phosphoethanolamine group linked to (the) 3 position of *(the)* HepII moiety.

2. The Examiner, in paragraph 13 of the Final Office Action mailed August 20, 2008 maintained the rejection of claims 62, 66, and 78 made in paragraph 10(e) of the Office Action mailed July 30, 2007 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner stated:

> "Applicants state that they disagree with the rejection and that they have amended claims 62, 66 and 78 to expedite prosecution. Applicants have amended the claims to specify the source of the recited outer core. However, the claims continue to include the limitation 'a presence of an outer core LPS'. Since the specification indicates the presence of no more than one outer core in the LPS of *Neisseria meningitidis* immunotypes L1, L3 and L7 to L12, it is suggested that Applicants replace the above-identified limitation with the limitation --the presence of outer core LPS--.
>
> Claims 62, 66, and 78 are herein canceled, thereby rendering this rejection moot.

3. The Examiner, in paragraph 14 of the Final Office Action mailed August 20, 2008 maintained the rejection of claims 75 and 81 made in paragraph 10(f) of the Office Action mailed July 30, 2007 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner alleged that:

> "Applicants state that they disagree with the rejection and that they have the amended claims to expedite prosecution. However, while amendments have been made to claims 64, 65, 68, 69, 74 and 80, claims 75 and 81 continue to include the limitation: 'a *Neisseria* LPS'. The rejection stands."
>
> Claims 75 and 81 have been canceled herein, thereby rendering this rejection moot. Applicants also note, however, that the new claims submitted herein make no reference to the objected term "a *Neisseria* LPS."

4. The Examiner, in paragraph 15 of the Final Office Action mailed August 20, 2008 maintained the rejection of claims 48, 55, 70, and 76 made in paragraph 10(g) of the Office Action mailed July 30, 2007 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner stated that:

> "Applicants state that they provided an infant rat model, considered by those skilled in the art, valuable for the development and preclinical assessment of meningococcal vaccines. Applicants maintain that the infant rat model provides valuable, clear, *in vivo* information concerning the interactions of the vaccine with the innate, humoral and cellular immune systems. Applicants assert that infection of infant rats for assessing passive protection has been described in such detail that the claim limitation of claims 48, 55, 70 and 76 is definite. Applicants' arguments have been carefully considered, but are not persuasive. Instant claims continue to include the limitation: 'capable of conferring passive

protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain' without specifying in whom the recited antibody is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain. Contrary to Applicants' argument, the claims do not recite that the antibody is capable of conferring passive protection in infant rats against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain. Furthermore, as presented currently, the limitation identified above is vague and repugnant because the art recognizes *galE* mutant of *Neisseria meningitidis* to be an avirulent or non-pathogenic strain that does not require or necessitate passive protection. As set forth previously, the state of the art recognizes that *galE* mutation dramatically alters the virulence potential of meningococci and that *galE* mutants of *Neisseria meningitidis* are "both serum sensitive and **avirulent** for infant rats", the avirulence being independent of encapsulation. See the first full sentence in left column on page 164 and the first two full sentences under 'Discussion' of Vogel *et al. (Microbial. Immunol.* 186: 159-166, 1997) (Vogel *et al.*, 1997, already of record)."

Claims 48, 55, 70 and 76 have been canceled herein, thereby rendering the rejection as now moot. Applicant further notes that the new claims submitted herein do not incorporate the phrase 'capable of conferring passive protection against a galE mutant of an L3 immunotype *Neisseria meningitidis* strain' that had been rejected by the Examiner.

5. The Examiner, in paragraph 16 of the Final Office Action mailed August 20, 2008 has maintained the rejection of claims 62-69, 72-75, and 78-81 made in paragraph 10(h) of the Office Action mailed July 30, 2007 under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claims 62-69, 72-75, and 78-81 have been canceled herein, thereby rendering this rejection moot.

Rejection under 35 USC §102(b)

The Examiner has maintained the rejection of claims 48, 55, 62-70,72-76, and 78-81 made in paragraph 11 of the Office Action mailed July 30, 2007 under 35 U.S.C §102(b) as being anticipated by van der Ley et al. (Mol. Microbiol. 19: 1117-1125, 1996, already of record) as evidenced by Poolman J.T. (Infectious Agent and Disease 4: 13-28, 1995, already of record) and Vogel et al. (Microbiol. Immunol. 186: 159-166, October 1997, already of record) or van der Ley et al. (Vaccine 13: 401- 407, 1995, already of record) (van der Ley et al., 1995). Applicants traverse this rejection.

The Examiner states in the Final Office Action at page 14:

"Applicants' arguments have been carefully considered, but are not persuasive. As set forth previously, it is noted that the instant specification identifies H44/76 strain of *Neisseria meningitidis* as an L3 immunotype strain. It is

well known that *galE* mutant lacks outer core structures. See the specification on page 6; see the Table on page 36, and first paragraph on page 47. It is further noted that the inner core of a *Neisseria* LPS comprised in the recited immunogenic composition is not required to be from a *galE Neisseria* mutant."

Applicants' position is that it is irrelevant whether the cited references teach the eliciting of an antibody using a *galE* mutant of *Neisseria meningitidis,* even if one of the raised antibodies binds to the *galE* mutant *and* wild-type strains. Applicants acknowledge the listed observations or results taught in the cited van der Ley et al. reference, as stated by the Examiner, as follows:

(1) "...a method of immunizing experimental host animals with an outer membrane complex preparation from a *galE* mutant of strain H44/76 (L3 immunotype) of *Neisseria meningitidis* mixed in an adjuvant, and the selection of positive hybridomas using *galE* LPS as the coating antigen in ELISA. See paragraph bridging pages 1122 and 1123; and last full paragraph on page 1123."

(2) "The last full paragraph on page 1123 of van der Ley *et al.* expressly taught the following:

> "Four new mAbs directed against *galE* mutant LPS, i.e. MN3 1A4.3 1, MN3 1D8.5 1, MN3 1E8.41 and MN3 1G9.19, were isolated after immunization with outer membrane complexes (OMCs) from a *galE* mutant derivative of strain H44176. . . .. Positive hybridomas were selected using ELISA with *galE* LPS as the coat antigen."

(3) "....mAbs have....been isolated after immunization with *galE* LPS.....one of the four new mAbs also binds.....to the LPS of the *galE* mutant *and* wild-type strains. See (paragraph bridging pages 1122 and 1123 of van der Ley *et al.*). These results show that by using mutant LPS, structures in the inner core, which are not normally immunogenic, can now become so. When also accessible in wild-type strains, such epitopes could be valuable for vaccine purposes, because the inner core is more conserved among different strains and is not known to contain host-identical epitopes."

The Examiner has also stated that the prior art LPS-containing immunogen administered to experimental animals is derived from the *galE* mutant of the same identical H44/76 strain of *Neisseria meningitidis* that is used by Applicants to generate MAb B5 specific to the Neisserial inner core LPS. The Examiner further alleges the following, to which the present Applicants respond accordingly:

1. "Since the prior art immunogenic inner core-containing *galE* mutant LPS or the prior art inner core-containing ***outer membrane complex preparation*** from the *galE* mutant of strain H44/76 of *Neisseria meningitidis* ***are not fully purified, they are expected to comprise a contaminant protein or peptide naturally conjugated thereto***. [Emphasis added]

The Examiner concedes, therefore, from the outset that the prior art inner core derived from the particular mutant *Neisseria meningitidis* strain comprises peptide or protein impurities

which might be expected to be possible sources of immunogens besides the epitope that is clearly identified in the specification, and claimed, in the present application. The cited prior art not only has failed to identify the epitope that is the subject matter of the present application, but further teaches the use of an impure immunogen that can be expected to give rise to antibodies directed to the impurities and not the target epitope of the present application. Resolution of such a possible complex of antibodies generated from an impure immunogen would require the undue experimentation and cannot be deduced from the data of the alleged prior art.

2. "That the prior art LPS-containing immunogen derived from the *galE* mutant of the same identical H44176 strain of *Neisseria meningitidis* as that used by Applicants comprises a phosphoethanolamine moiety linked to position 3 of HepII moiety is inherent from the teachings of van der Ley *et al.* in light of what is well known in the art. For instance, Poolman JT disclosed of the existence of phosphoethanolamine moiety linked to position 3 of Hep2 moiety of the inner core of the lipopolysaccharide of native and *galE* immunotype L3 of *Neisseria meningitidis*. See Figure 2."

The cited prior art reference of van der Ley et al., describes the use of an immunogen that is impure, as noted by the Examiner, and does not identify the epitope that is the subject matter of the present application. Poolman et al identifies, within the structure of the inner core of the lipopolysaccharide of the *galE* immunotype L3 of *Neisseria meningitides,* existence of a phosphoethanolamine moiety linked to position 3 of Hep2 moiety, but again does not identify the phosphoethanolamine as the target epitope. Accordingly, any inference that they are one and the same can only be by a hindsight analysis by the Examiner.

3. "That the prior art LPS-containing immunogen derived from the *galE* mutant of lacks an outer core in the LPS is also inherent from the teachings of the prior art in light of what is known in the art. For instance, Vogel *et al.* showed that *galE* mutation results in a truncated LPS that lacks the outer core (see Figure 1). Similarly, van der Ley *et al.* (1995) taught that *galE* deletion in *Neisseria meningitidis* leads to the synthesis of galactose-deficient LPS in addition to teaching the desirability of lack of lacto- N-neotetraose structure in a *galE* vaccine strain (see paragraph bridging page 403)."

The above statement by the Examiner fails to indicate what relevance details of the outer core have to the structure and identity of the inner core epitope that is the subject matter of the present application. The epitope claimed in the newly submitted claims of the present application is defined in structural terms and by being specifically reactive with a defined monoclonal antibody. The issue of the outer core of the LPS is of concern only with regard to the ability of an inner core of the LPS to generate inner core-specific antibodies, and does not pertain to the identity of the target epitope.

The Examiner erroneously arrives at a conclusion from these statements that the prior art method ***necessarily*** elicits an antibody that: (i) has the intrinsic ability to recognize *Neisseria meningitidis* immunotypes L1, L3 and L7-L12 in the presence or absence of an outer core LPS; and (ii) the intrinsic capability of conferring passive protection against a *galE* mutant of an *Neisseria meningitidis* L3 immunotype strain, even though the cited alleged prior art provides no teachings or suggestions that any antibody generated by their methods can distinguish the immunotypes L1, L3 and L7-L12 from other immunotypes of Neisseria meningitidis.

Although the Examiner does correctly state that accessibility to the recited antibody in the presence of a capsule of *Neisseria meningitidis* is not a property of the recited antibody, but rather is an intrinsic property of the inner core LPS of the recited immunotypes or naturally occurring strains of *Neisseria meningitidis,* Applicants respectfully note that the references cited by the Examiner apply to the LPS as a whole, whereas the present application teaches that accessibility to an immunotype-specific antibody is a property of the targeted epitope itself, the epitope being taught only by, of the present application, and claimed in the newly submitted claims thereof.

Applicants object to the sweeping conclusory statement by the Examiner that the prior art method, which elicits antibodies both to the *galE* mutant *and* wild-type strains of *Neisseria meningitidis,* "is expected to necessarily immunize the murine host against 'a majority' of naturally occurring strains of *Neisseria meningitidis* in light of what was known in the art at the time of the invention" The cited alleged prior reference of van der Ley provides no teaching that an antibody specifically binding the epitope defined and claimed in the present application can distinguish a specific group of immunotypes other than L3, or that a majority of Neisseria immunotypes will be recognized by such an antibody. Applicants note that the cited reference of Poolman et al, for example, teaches ***only*** that the L3 immunotypes alone account about 80% of (i.e., majority of) meningococcal ***isolates*** from group B cases, not immunotypes.

4. "The Office's position that van der Ley's method is the same as the Applicants' method is based upon the fact that the prior art method uses the inner core-containing immunogen composition from the same L3 immunotype H44/76 strain of *N. meningitidis* as the one used by Applicants in the instant specification. Therefore, the prior art inner core-containing immunogen is expected to necessarily have the same intrinsic structure and the same immunogenic, protective, and/or cross-reactive properties as that of the Applicants' immunogenic composition."

Applicants note, however, that the Examiner has stated that the LPS preparation used to elicit antibodies was inherently impure (see above) with attached proteinaceous fragments. In addition, none of the cited alleged prior art references identify the specific epitope as taught and

claimed in the present application. The Examiner does not, and cannot, point to any statement in the cited references that preclude the possibility of the methods of the cited references from giving rise to antibodies NOT targeting the epitope as taught and claimed in the present application.

Applicants therefore, have met the burden to show a novel or unobvious difference between the claimed method and the method of the prior art, namely a well-defined epitope structure not previously identified as the target epitope of the methods taught and claimed in the present application (i.e., the prior art method has not been shown to induce the same functional effects as the claimed method, namely to bind to the *specific* epitope as taught and claimed in the present application).

Applicants maintain that the cited references, alone, or in combination do not teach the epitope, and the methods of use thereof, as taught and claimed in the present application. The specific identity of the epitope that is the subject matter of the present application cannot be deduced from any, some, or all of the cited references. It is the identification of the claimed epitope that is the surprising and therefore unanticipated teaching of the present application, and there is no showing, even remotely, that the cited references had knowledge of the identity of the specific epitope. Knowledge of the structure of the inner and outer cores of the lipopolysaccharide of *Neisseria*, in and of itself, in the absence of the experimental data disclosed in the specification of the present application cannot identify the defined epitope as taught and claimed in the present application. Therefore, the van der Ley reference, even when it is attempted to show that unrecited characteristics are inherent by referring to the Vogel et al., Poolman et al., van der Ley et al. (1995) and van der Ley et al. (1996) references, fails to teach each and every element of the new claims as submitted herein in the present application

5. The Examiner further states:

> "To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268,20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. Atlas Powder Co. v. IRECO Inc., 190 F.3d 1342, 1349,5 1 USPQ2d 1943, 1948 (Fed. Cir. 1999). Also note that the critical date of extrinsic evidence showing a universal fact need **not** antedate the filing date. See MPEP 2124."

Applicants maintain, however, the allegation that the Office has not provided sufficient basis to reasonably support the determination that the inherent characteristics necessarily flow from the disclosure of the applied prior art. Without the experimental results, as taught in the specification of the present application, one of ordinary skill in the art would not be able to identify the specific target epitope as taught and claimed in the present application from a mere examination of the structure of the inner and outer cores of the *Neisseria* lipopolysaccharide as taught by the cited alleged prior art references. The isolation by identification of the target epitope is neither self-evident nor predictable from the knowledge at the time of the present invention.

6. "With regard to Applicants' arguments, whether or not HC-L3 and ES-L3 strains of van der Ley et al. are stable L3 negative mutants containing an erythromycin resistance marker, is irrelevant. What is relevant is that the galE mutant of strain H44/76 (L3 immunotype) of *Neisseria meningitidis* used by van der Ley et al. and the galE inner core-containing immunogenic composition therefrom are the same as the ones used by Applicants."

While the *galE* mutant of strain H44/76 (L3 immunotype) of *Neisseria meningitidis* was the same in the van der Ley reference and the present disclosure, the Examiner has noted the impure nature of the van der Ley inner core preparation, which raises the possibility of multiple antibodies recognizing a multiplicity of antigens being generated. Van der Ley has failed to identify the target epitope as claimed in the present application, and therefore does not exclude the possibility that another epitope is the target of their antibodies. Thus, the *galE* mutation is irrelevant as to the structure and definition of the target epitope as defined in the newly submitted claims.

7. "With regard to Applicants' argument that MAb B5 was obtained by immunizing mice with a galE mutant of Neisseria meningitidis H44/76 (B.15.P. 1.7.16 immunotype L3), it should be noted that 'MAb B5' is not currently a claim limitation. The generic limitation 'antibody' in the instant base claims encompasses a polyclonal antibody, and a monoclonal antibody other than MAb B5."

The newly submitted claims 82-100 now refer to the monoclonal antibody B5, and therefore this argument by the Examiner is rendered moot.

8. "With regard to Applicants' argument that monoclonal antibodies used by van der Ley *et al.* were initially raised after immunization with outer membrane complexes (OMCs) whereas the claims of the present application are directed at eliciting in a host an antibody that specifically binds to an inner core of lipopolysaccharide by administering to a host an immunogenic composition comprising an inner core of a *Neisseria* lipopolysaccharide (LPS) substantially free from outer core lipopolysaccharide, the following must be noted:

"The limitation in the instant base claims 'immunogenic composition comprising' represents open claim language. The transitional term 'comprising' is synonymous with 'including', 'containing', or 'characterized by' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686,210 USPQ 795, 803 (CCPA 1981);* and *Exparte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ('comprising leaves 'the claim open for the inclusion of unspecified ingredients even in major amounts'). Furthermore, the recited 'a first inner core of a Neisseria lipopolysaccharide' is not required to be purified, not even required to be isolated, and therefore encompasses inner core LPS naturally present in association with van der Ley's immunogenic OMPC from *galE* mutant of *Neisseria meningitidis* H44176 (B.15 .P. 1.7.16 immunotype L3). The inner core LPS lacking outer core LPS is 'comprised' within van der Ley's immunizing composition that comprises OMPC from *galE* mutant of *Neisseria meningitidis* H44176 (B.15.P. 1.7.16 immunotype L3). As recited currently, the presence of the prior art OMPC from *galE* mutant of *Neisseria meningitidis* H44176 (B.15.P. 1.7.16 immunotype L3) is not excluded from the immunogenic composition of the instant claims. For the reasons delineated above, the teachings of van der Ley *et al.* anticipate the instant claims."

Claims 48, 55, 62-70, 72-76, and 78-81 are canceled herein and new claims 82-99 are submitted. The new claims now use the language "consisting essentially of" the defined epitope structure that has not been identified, isolated, or referred to by the cited alleged prior art references. Accordingly, Applicants maintain that the cited van der Ley reference, even in light of the other cited references, does not teach the use of a composition that has as its key element the epitope as defined by the present application. Applicants therefore request withdrawal of the rejection.

New Rejection(s) Necessitated by Applicants' Amendment-Rejection(s) under 35 U.S.C §112, First Paragraph (New Matter)

Claims 48, 55, 62-70, 72-76, and 78-81 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner stated that:

"Claims 48, 55, 70, and 76, as amended, include the new limitation: 'a first inner core of a *Neisseria* lipopolysaccharide'. Claims 70 and 76, as amended, include the new limitations: 'a second' inner core LPS of a majority of naturally

occurring strains of *Neisseria meningitidis*. Claims 48 and 55, as amended, include the new limitations: 'a second inner core of lipopolysaccharide of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11, and L12'. Claims 62, 63, 66, 67, 72, 73, 78 and 79 include the new limitation: 'said second' inner core. Claims 64, 65, 68, 69, 74, 75, 80 and 8 1 include the new limitation: 'said first' inner core."

Claims 48, 55, 62-70, 72-76, and 78-81 are herein canceled and new claims submitted, thereby rendering the rejection moot. None of the newly submitted claims include the language objected to. Applicants therefore request that this rejection be withdrawn.

Rejection(s) under 35 U.S.C. §112, Second Paragraph

Claims 48, 55, 62-70, 72-76, and 78-81 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner stated in the Final Office Action that:

"(a) Claims 48, 55, 70 and 76, as amended, are indefinite in the limitation: 'composition comprising a first inner core of a Neisseria lipopolysaccharide (LPS) **and** is substantially free from outer core lipopolysaccharide' [Emphasis added], because it is unclear whether it is the immunogenic composition that is substantially free from outer core lipopolysaccharide, or whether it is the recited inner core that is substantially free from outer core lipopolysaccharide. If the latter is intended, it is suggested that Applicants replace the limitation 'and' with the limitation --which is--.

(b) Claims 48, 55, 70 and 76, as amended, are indefinite in the limitation: 'composition comprising a first inner core . . . . . and substantially free from outer core lipopolysaccharide'. The term 'substantially free' is a relative term which is not specifically defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the claim. What amount, length, or element of the recited outer core lipopolysaccharide has to be absent in the recited composition such that the composition qualifies as a composition that is 'substantially free from outer core lipopolysaccharide' is unclear.

(c) Claims 63, 67, 73 and 79, as amended, are indefinite because these claims lack proper antecedent basis in the limitation: 'bacterial capsule of a Neisseria meningitidis strain'. These claims depend from claims 48, 55, 70 and 76 respectively, which recite 'Neisseria meningitidis immunotypes L1, L3, L7, L8, L9, L10, L11 and L12'. For proper antecedence, and to be similar to the correction/amendment made to claims 62, 66, 72 and 78, it is suggested that Applicants replace the above-identified limitation with the limitation: --capsule of said Neisseria meningitidis immunotypes L1, L3, L7, L8, L9, L10, L11 and L12--.

(d) Claims 55, 62-70, 72-76 and 78-8 1, which depend directly or indirectly from claims 48, 55, 70 and 76, are also rejected as being indefinite because of the indefiniteness identified above in the base claims."

Claims 48, 55, 62-70, 72-76, and 78-81 are herein canceled and new claims submitted, thereby rendering the rejection moot. None of the newly submitted claims include the language objected to. Applicants therefore request that this rejection be withdrawn.

Remarks

Examiner has requested that in the claim language used in claims 48, 55 and 70 Applicants replace the limitation 'whereby' in claims 55 and 76 with the limitation --wherein--. To be consistent with the italicized limitation 'galE' used all through the instant specification and in the art, it is suggested that Applicants replace the non-italicized limitation 'galE' in the instant claims with the italicized limitation --galE--.

Claims 48, 55, 62-70, 72-76, and 78-81 are herein canceled and Applicants note that the new claims submitted herein now have language consistent with the Examiner's requirements.

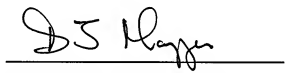
CONCLUSION

In light of the foregoing amendments and for at least the reasons set forth above, Applicants submit that all objections and/or rejections have been traversed, rendered moot, and/or accommodated. Favorable reconsideration and allowance of the present application and all pending claims are hereby requested.

Furthermore, any and all findings of well-known art and official notice, or statements interpreted similarly, should not be considered well known since the Office Action does not include specific factual findings predicated on sound technical and scientific reasoning to support such conclusions.

If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (770) 933-9500.

Respectfully submitted,



David J. Hayzer, Reg. No. 43,329

THOMAS, KAYDEN, HORSTEMEYER & RISLEY, L.L.P.

Suite 1500

600 Galleria Parkway S.E.

Atlanta, Georgia 30339

(770) 933-9500